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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/976,929	10/11/2001	Anita Melikian-Badalian	AVMX-012/01US	2050

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EXAMINER	
COLEMAN, BRENDA LIBBY	

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 04/21/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/976,929	MELIKIAN-BADALIAN, ANITA	
	Examiner	Art Unit	
	Brenda Coleman	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-35* is/are pending in the application.

4a) Of the above claim(s) *4* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3 and 5-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/18/02 & 9/30/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-35 are pending in the application.

Election/Restrictions

1. Applicant's election without traverse of Group II in Paper filed December 11, 2003 is acknowledged.

2. Claim 4 is withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper filed December 11, 2003.

3. Claims 1-3, 6-8 and 10-35 are rejected as being drawn to an improper Markush group. The recited compounds, while possessing a common utility, differ widely in structure and are not art-recognized equivalents and are thus, independently distinct for the reasons set forth in the restriction requirement.

Oath/Declaration

4. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application, by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:
The specification to which the oath or declaration is directed has not been adequately identified. See MPEP § 601.01(a).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 10-35 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The scope of the method claims is not adequately enabled solely based on inhibiting P-glycoprotein-mediated transport provided in the specification. Recent transport studies cited in the European Journal of Pharmaceutical Sciences indicate that transport studies remain scarce thus enabling the construction of a useful tool for the screening of potential P-gp substrates and inhibitors. For the screening of P-gp substrates, better model systems have to be developed.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. In addition to other diseases and/or disorders, which are difficult to treat these claims call for the treatment of tumors. However, there never has been a compound capable of treating tumors generally. There are compounds that treat a range of tumors, but no one has ever been able to figure out how to get a compound to treat tumors generally, or even a majority of tumors. Thus, the existence of such a "silver bullet" is contrary to our present understanding in oncology. Even the most broadly effective antitumor agents are only effective against a small fraction of the vast number of different cancers known. This is true in part because cancers arise from a wide variety of sources, such as viruses (e.g. EBV, HHV-8, and HTLV-1), exposure to

chemicals such as tobacco tars, genetic disorders, ionizing radiation, and a wide variety of failures of the body's cell growth regulatory mechanisms. Different types of cancers affect different organs and have different methods of growth and harm to the body, and different vulnerabilities. Thus, it is beyond the skill of oncologists today to get an agent to be effective against cancers generally, evidence that the level of skill in this art is low relative to the difficulty of such a task.

Where the utility is unusual or difficult to treat or speculative, the examiner has authority to require evidence that tests relied upon are reasonably predictive of in vivo efficacy by those skilled in the art. See In re Ruskin, 148 USPQ 221; Ex parte Jovanovics, 211 USPQ 907; MPEP 2164.05(a).

Patent Protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. Tossing out the mere germ of an idea does not constitute enabling disclosure. Genentech Inc. v. Novo Nordisk 42 USPQ2d 1001.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

6. Claims 1-3 and 5-35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following reasons apply:

a) Claims 1, 2, 6 and 10-35 are vague and indefinite in that it is not known what is meant by the definition of R_3, R_4, R_5, R_6, R_7, and R_8 where R_3, R_4, R_5, R_6,

R_7, and R_8 is $CO(CH_2)_n$ which is not valence satisfied. It is not known what else is bound to the moiety.

b) Claims 1, 2, 6 and 10-35 are vague and indefinite in that it is not known what is meant by the variable A, which is not defined in the claim.

c) Claims 1, 2, 6 and 10-35 are vague and indefinite in that it is not known what is meant by contiguous carbons.

d) Claims 1-3, 6-8 and 10-35 are vague and indefinite in that it is not known what is meant by the definition of R_9 where R_9 is alkylene, alkenylene, alkylidene or alkynylene all of which are divalent moieties, however, the variable R_9 is not.

e) Claims 1-3, 6-8 and 10-35 are vague and indefinite in that it is not known what is meant by the definition of R_{10} and R_{11} where R_{10} and R_{11} are alkylene, alkenylene, alkylidene or alkynylene as well as phenylene and benzylene all of which are divalent moieties, however, the variables R_{10} and R_{11} are not.

f) Claims 1-3, 6-8 and 10-35 are vague and indefinite in that it is not known what is meant by the definition of R_{10} and R_{11} where R_{10} and R_{11} are $S(O)_q(R_{14})$, $C(O)NH(R_{14})$ or $C(O)_q(R_{14})$ all of which may be linear or branched, however, it is not known how $S(O)_q(R_{14})$, $C(O)NH(R_{14})$ or $C(O)_q(R_{14})$ of the variables R_{10} and R_{11} can be linear or branched.

g) Claims 1-3, 6-8 and 10-35 are vague and indefinite in that it is not known what is meant by the definition of R_{17}, R_{18}, R_{19} where R_{17}, R_{18}, R_{19} are $CO(CH_2)_n$ which is not valence satisfied. It is not known what else is bound to the moiety.

h) Claim 2 recites the limitation "$CH_2(O)$" in the definition of X. There is insufficient antecedent basis for this limitation in the claim.

i) Claim 5 recites the limitation "piperazin" in the nomenclature of the species. There is insufficient antecedent basis for this limitation in the claim.

j) Claim 5 recites the limitation "ethanone" in the nomenclature of the species. There is insufficient antecedent basis for this limitation in the claim.

k) Claim 9 recites the limitation "benzyl" in the nomenclature of the species. There is insufficient antecedent basis for this limitation in the claim.

l) Claims 10, 19, 20-24, 29-33, 35 and claims dependent thereon are vague and indefinite in that it is not known what is meant by a compound of Formula I where there is no Formula I in the claim.

m) Claim 11 is vague and indefinite in that it is not known what is meant by a compound of Formula I selected from the group presented in Table I. Reference to Table I does not permit claim 11 to stand alone nor describe the compounds of Formula I.

n) Claim 19 provides for the use of a compound of Formula I, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

o) Claim 20 is a substantial duplicate of claim 1 as the only difference is a statement of intended use, which is not given material weight. Note In re Tuominen 213 USPQ 89.

p) Claim 23 is a substantial duplicate of claim 32 as the only difference is a statement of intended use, which is not given material weight. Note In re Tuominen 213 USPQ 89.

q) Claims 10-35 are vague and indefinite in that the claim provides for the use of claimed compounds, but the claim does not set forth any steps involved in determining which are the diseases capable of being mediated by P-glycoprotein transport. Determining whether a given disease responds or does not respond to such an inhibitor will involve undue experimentation. Suppose that a given drug, which has inhibitor properties in vitro, when administered to a patient with a certain disease, does not produce a favorable response. One cannot conclude that specific disease does not fall within this claim. Keep in mind that:

A. It may be that the next patient will respond. No pharmaceutical has 100% efficacy. What success rate is required to conclude our drug is a treatment? Thus, how many patients need to be treated? If "successful treatment" is what is intended, what criterion is to be used? If one person in 10 responds to a given drug, does that mean that the disease is treatable? One in 100? 1,000? 10,000? Will the standard vary depending on the current therapy for the disease?

B. It may be that the wrong dosage or dosage regimen was employed. Drugs with similar chemical structures can have markedly different pharmacokinetics and metabolic fates. It is quite common for pharmaceuticals to work and or be safe at one dosage, but not at another that is significantly higher or lower. Furthermore, the dosage regimen may be vital --- should the drug be given e.g. once a day, or four times in divided dosages? The optimum route of administration cannot be predicted in advance. Should our drug be given as a bolus iv or in a time release po formulation. Thus, how many dosages and dosage regimens must be tried before one is certain that our drug is not a treatment for this specific disease?

C. It may be that our specific drug, while active in vitro, simply is not potent enough or produces such low concentrations in the blood that it is not an effective treatment of the specific disease. Perhaps a structurally related drug is potent enough or produces high enough blood concentrations to treat the disease in question, so that the first drug really does fall within the claim. Thus, how many different structurally related inhibitors must be tried before one concludes that a specific compound does not fall within the claim?

D. Conversely, if the disease responds to our second drug but not to the first, both of which are inhibitors in vitro, can one really conclude that the disease falls within the claim? It may be that the first compound result is giving the accurate answer, and that the success of second compound arises from some other unknown property, which the second drug is capable. It is common for a

drug, particularly in anti-cancer or multi-drug resistance, to work by many mechanisms. The history of psychopharmacology is filled with drugs, which were claimed to be a pure receptor XYX agonist or antagonist, but upon further experimentation shown to affect a variety of biological targets. In fact, the development of a drug for a specific disease and the determination of its biological site of action usually precede linking that site of action with the disease. Thus, when mixed results are obtained, how many more drugs need be tested?

E. Suppose that our drug is an effective treatment of the disease of interest, but only when combined with some totally different drug. There are for example, agents in antiviral and anticancer chemotherapy, which are not themselves effective, but are effective treatments when the agents are combined with something else.

Consequently, determining the true scope of the claim will involve extensive and potentially inconclusive research. Without it, one skilled in the art cannot determine the actual scope of the claim. Hence, the claim is indefinite.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

7. Claim 19 is rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper

definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brenda Coleman whose telephone number is 571-272-0665. The examiner can normally be reached on 9:30-6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mukund Shah can be reached on 571-272-0674. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Brenda Coleman

Brenda Coleman
Primary Examiner Art Unit 1624
April 16, 2004